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Case Report

Ameloblastic Fibrosarcoma of the Jaw: Case Report, Genetic Profiling, and Literature Review

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Keywords
Ameloblastic fibrosarcoma · NTRK1 · Ameloblastic Fibroma · BRAF · Next-generation sequencing

Abstract
Ameloblastic fibrosarcoma (AFS) is considered a malignant progression resulting from dysplastic changes in an ameloblastic fibroma (AF). Both tumors are extremely rare, with only a few cases reported in the scientific literature. Notably, BRAF mutations have been identified in ameloblastomas, suggesting a connection between ameloblastic morphology and BRAF mutations, as AF is believed to be the precursor neoplasm leading to AFS. In this study, we present a case of AFS in a 25-year-old male. The tumor tissue underwent molecular analysis, specifically next-generation sequencing (NGS) using the Oncomine Comprehensive Assay v3 System. The analysis revealed pathogenic mutations in TP53 and RB genes, as well as copy number gains in NTRK1, MDM4, and BRAF. Additionally, we provide a summary of the literature's findings from the analysis of 107 previously reported AFS cases. Our findings suggest the existence of a molecularly distinct subtype, emphasizing the importance of comprehensive molecular testing for these patients.

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Introduction

The most common tumor of the jaw is ameloblastoma, a benign odontogenic tumor. Malignant odontogenic tumors are classified by the WHO as both carcinomas and sarcomas, while mixed epithelial and mesenchymal tumors of the odontogenic tissue are rare. Ameloblastic fibrosarcoma (AFS) was first described in 1887 [1], and it is an aggressive malignant tumor consisting of a biphasic benign odontogenic epithelium with a sarcomatous mesenchymal component [2–4]. This condition has a slight male predominance of 1.5–1.6. AFS is believed to be a malignant spectrum of the dysplastic changes arising in ameloblastic fibroma (AF). Both tumors are exceedingly rare, with 107 AFS cases reported in the literature [5–7].

Molecular characterization has reported BRAF mutations in ameloblastomas, and hence, ameloblastic morphology has also been found to harbor BRAF mutations [8]. On the other hand, molecular landscape of AFS tumors has rarely been reported, while one paper has highlighted frequent BRAF V600E and occasional NRAS mutations reported among 7 AFS cases [9].

Case Report

An otherwise healthy 25-year-old man presented to the hospital with left mandible swelling which persisted for 1 month. The patient also reported significant weight loss and lower lip numbness. He was admitted for work-up, and a computed tomography (CT) facial examination was performed, revealing an osteolytic lesion that was detected on the left side of the mandible. The lesion showed disruption of the cortical outline with periosteal elevation and a sublingual soft tissue extension (shown in Fig. 1a, b). The mass effect also caused displacement of the medial mylohyoid hypoglossal muscle. Magnetic resonance imaging with contrast was also performed, revealing a 6.5 cm mass causing malalignment of the left lower third molar tooth with an associated sizable soft tissue component measuring up to 2.3 cm in thickness. Lymph node involvement was also identified inferior to the lesion (shown in Fig. 1c, d). A positron emission tomography scan with FDG update was performed, and the highlighted tumor is shown (shown in Fig. 1e). Histopathological examination revealed interspersed islands of benign odontogenic epithelium with peripheral palisading in a background of hypercellular spindle to pleomorphic "sarcomatous" component (shown in Fig. 2a). The pleomorphic sarcomatous component was predominating with necrosis (shown in Fig. 2b). Higher power magnification showed nuclear pleomorphism and hyperchromasia with abundant mitosis (shown in Fig. 2c, d). Immunohistochemical (IHC) staining was positive for vimentin and P53, with few cells showing dot-like positivity for desmin. The tumor was negative for muscular markers such as myogenin, Myo-D1, and muscle-specific-actin (MSA). CK5/6 was positive in the epithelial component. The Ki-67 proliferative index showed 40% staining of malignant cells. BRAF IHC staining was also performed, and the results were negative. The diagnosis of AFS was confirmed. Patient's schematic timeline is summarized in Figure 3.

Genetic Analysis

The tumor tissue was sent for molecular analysis, and next-generation sequencing (NGS) was performed using the Oncomine Comprehensive Assay v3 System, a targeted assay that enables the detection of relevant single nucleotide variations (SNVs), copy number variations (CNVs), gene fusions, and indels from 161 genes as previously described [10].

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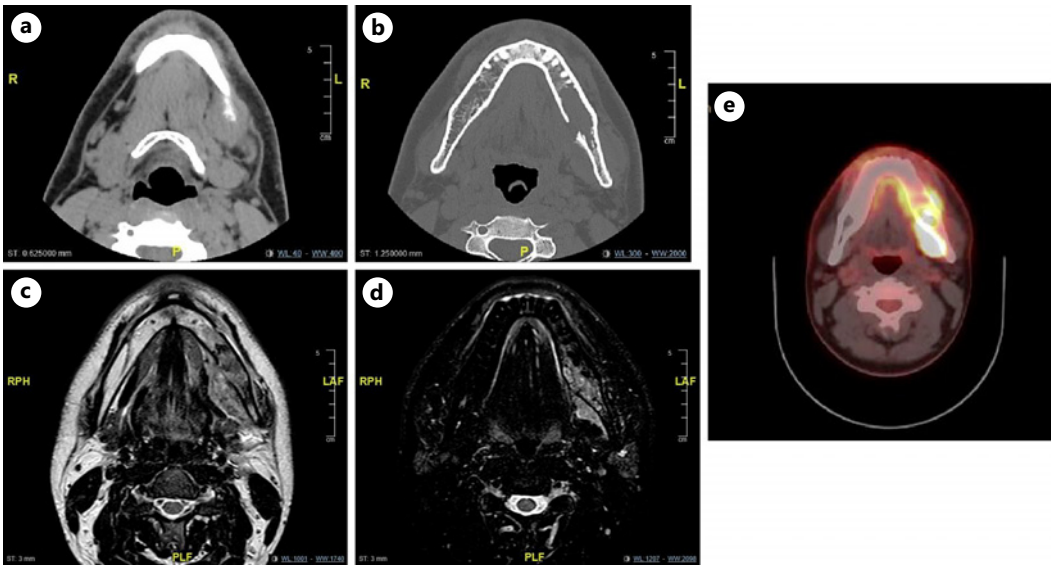

Fig. 1. **a** CT of the facial region with the bone window. **b** CT of the facial region with the soft tissue window. **c** MRI facial region showing enhancement. **d** MRI facial T2 with fat suppression. **e** PET scan with FDG uptake. MRI, magnetic resonance imaging; PET, positron emission tomography.

Discussion

Our analysis has identified neurotrophic tropomyosin-related kinase 1 (NTRK1) and BRAF (B-raf Proto-Oncogene) amplification at loci chr1.156785512 and chr7:140434535, respectively. A pathological missense mutation of TP53 causing an amino acid change of p.(R248W) encoding c.742C>T at locus chr17:7577539 was also identified, in addition to MDM4 (MDM4 Proto-Oncogene) amplification and retinoblastoma protein (RB1) frameshift insertion. Further details of the patient's report are summarized in Table 1. The patient presented at an advanced stage, and a biopsy and resection were conducted to assess the tumor's morphology and genetics. However, personalized targeted therapy was not administered during the treatment course, as the patient had already initiated conventional therapy.

AFS is a biphasic mesenchymal malignancy that was first described in 1887 [1]. Since its discovery, occasional reports have been published describing 107 cases. A systemic review was published in 2017 [11], highlighting the clinical features in 99 previously reported cases, although full data were missing in a handful of cases. In the period of 2017–2020, only 8 cases were reported, one in 2019 [12] and 7 in 2020 [9]. We have summarized the clinical findings of all 107 cases in Table 2. All patients ranged in age from 0.33 to 89 years old, with 30 years old being the median age. A slight majority of the cases occurred in males (56 males in comparison to 49 females), and the maximum size for each was between 0.7 cm and 14 cm in the maximum dimension. Furthermore, the majority of AFS tumors occurred in the mandible region (78 cases) as opposed to the maxilla region (27 cases). Regional and distant metastasis has been reported in few cases, while recurrence was more likely, with reports of 51 cases out of 94 showing regional recurrence.

Ameloblastomas have been characterized with BRAF mutations, and hence, ameloblastic morphology has also been found to harbor BRAF mutations [8]. Since AF is thought to be the precursor neoplasm giving rise to AFS [5], it has also been investigated for BRAF mutation via PCR by You et al. [13] The BRAF V600E point mutation was detected in all sixteen of their AF

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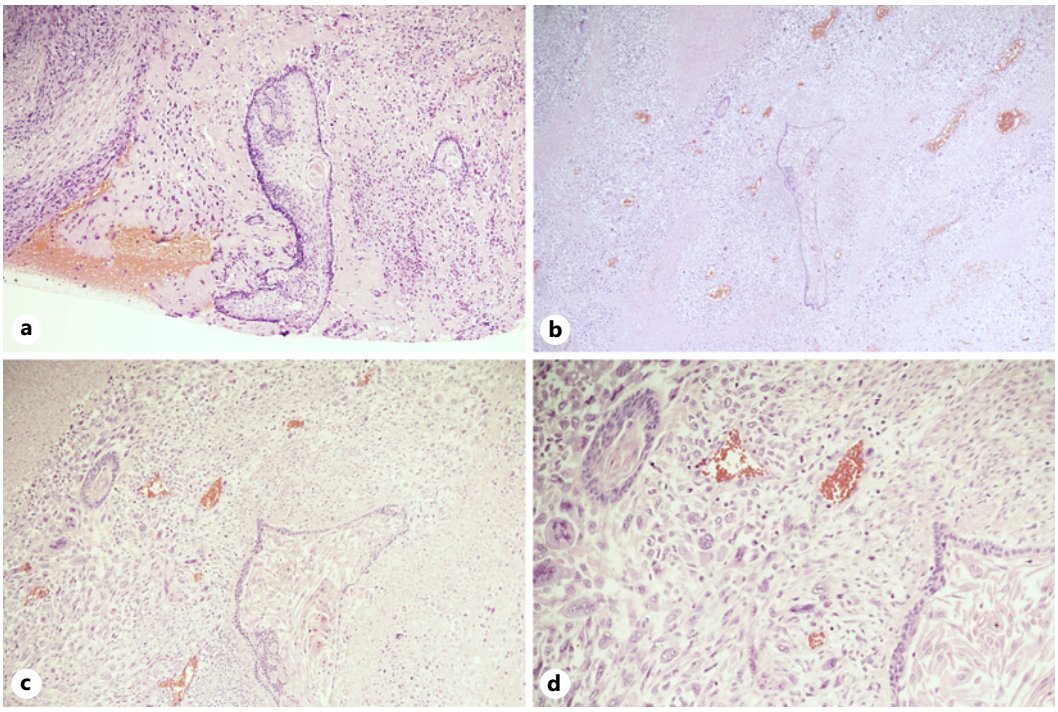

Fig. 2. **a** Bland-looking odontogenic epithelium with peripheral palisading with a spindle-to-pleomorphic "sarcomatous" component. **b** Benign-looking odontogenic epithelium with peripheral palisading mixed with a predominating malignant mesenchymal component and extensive tumor necrosis. **c**, **d** Higher magnification on the malignant mesenchymal component showing marked atypia and mitosis.

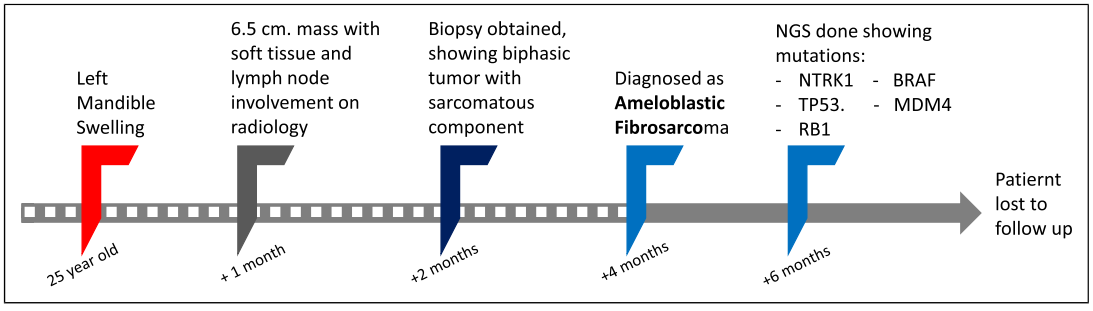

Fig. 3. A timeline schematic illustrating the patient's presentation, primarily with a left mandible swelling, which showed in radiology as a 6.5 cm mass, with soft tissue and lymph node involvement. On histopathology, the tumor showed benign odontogenic epithelium with a pleomorphic sarcomatous component. NGS was performed to check for genetic mutations.

cases. A case report published earlier this year reported the first molecular analysis of 7 AFS cases for BRAF/NRAS pathway mutations using amplicon-based massive parallel sequencing, targeting the gene mutations described previously in ameloblastoma. The BRAF V600E mutation was detected in 5/7 AFS cases with NRAS mutation in the 6th case, while the 7th case was wild-type. These researchers also confirmed their cases by BRAF VE1 IHC [9]. Our case showed negative BRAF IHC, which confirmed the molecular absence of a pathogenic BRAF V600E point mutation. Our case did show "amplification" in BRAF gene and lacked this

Table 1. Summary of the molecular findings of our case

Gene	Amino acid change	Coding	Locus	Allele frequency, %	Transcript	Variant effect
DNA sequence variants						
RB1	p.(A474fs)	c.220_221insAG	chr13: 48881488	77.22	NM_000321.2	Frameshift insertion
TP53	p.(R248W)	c.742C>T	chr17: 7577539	87.99	NM_000546.5	Missense

Gene	Locus	Copy number
Copy number variation		
NTRK1	chr1:156785512	5.38
MDM4	chr1:204494576	4.79
AKT3	chr1:243662992	4.98
BRAF	chr7.130434535	4.99

Table 2. Clinical findings in our case with Servato et al. [11], Maji et al. [12], and Agaimy et al. [9]

Number of cases	*n* = 107
Age	Range: 0.33–89 years
	Majority <65 years
	Median: 30 years
Gender	Males: 56
	Females: 49
Size	0.7–14 cm
Location	Maxilla: 27
	Mandible: 78
Regional metastasis	2/93 (not specified in Maji et al. [12], 2019)
Distant metastasis	6/94 (not specified in Maji et al. [12], 2019)
Recurrence	51/97 (not specified in Maji et al. [12], 2019)

specific point mutation. NTRK1 amplification (with the absence of NTRK2 and NTRK3 abnormalities) was also highlighted in the absence of any fusion (Table 1). This result indicates the futility of targeted BRAF and/or NTRK inhibitor therapy in some AFS cases, with molecular characterization being essential as a management step for these tumors [14, 15].

Multiple studies have emphasized the utilization of targeted therapy for uterine sarcomas, specifically leiomyosarcomas and endometrial stromal sarcomas. These studies have indicated that adjuvant chemotherapy does not confer significant benefits in terms of overall recurrence. Furthermore, genetic abnormalities in TP53, RB1, and other genes have been identified as the predominant factors in these types of sarcomas. However, there is still a critical need to explore precision medicine approaches and enhance our understanding of the biological aspects of sarcomas, which necessitates further investigation [16–18].

In conclusion, AFS is an exceptionally rare malignant tumor that develops from dysplastic changes in its precursor neoplasm, AF. Understanding the molecular mechanisms underlying this aggressive tumor is of utmost importance. By employing NGS, the detection of pathogenic mutations in TP53 and RB genes, along with copy number gains in NTRK1, MDM4, and BRAF, offers potential avenues for personalized therapy. The aim of this report was to provide a comprehensive understanding of AFS by examining previous case reports and conducting a thorough literature review. The findings emphasize the necessity for ongoing research in order to enhance the diagnosis and treatment of AFS. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000532014).

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

D.B. wrote the manuscript. M.A. supervised the study and performed the technical analysis. A.A. provided the clinical data. All authors discussed the results and contributed to the final manuscript.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article. Further inquiries can be directed to the corresponding author.

References

1 Heath C. Lectures on certain diseases of the jaws. Br Med J. 1887;2(1385):111–5.
2 Santos JN, Pinto LP, de Figueredo CR, de Souza LB. Odontogenic tumors: analysis of 127 cases. Pesqui Odontol Bras. 2001;15(4):308–13.
3 Soluk-Tekkeşin M, Wright JM. The world health organization classification of odontogenic lesions: a summary of the changes of the 2017 (4th) edition. Turk Patoloji Derg. 2018;34(1).
4 Wright JM, Soluk Tekkesin M. Odontogenic tumors: where are we in 2017. J Istanb Univ Fac Dent. 2017;51(3 Suppl 1):S10–30.
5 Chrcanovic BR, Brennan PA, Rahimi S, Gomez RS. Ameloblastic fibroma and ameloblastic fibrosarcoma: a systematic review. J Oral Pathol Med. 2018;47(4):315–25.
6 Munisekhar MS, Shylaja S, Kumar RV, Rao KA, Patil SR, Alam MK. Ameloblastic fibrosarcoma: a rarity? JPRAS Open. 2019;21:56–62.
7 Mohsenifar Z, Behrad S, Abbas FM. Epithelial dysplasia in ameloblastic fibrosarcoma arising from recurrent ameloblastic fibroma in a 26-year-old Iranian man. Am J Case Rep. 2015;16:548–53.
8 Brunner P, Bihl M, Jundt G, Baumhoer D, Hoeller S. BRAF p.V600E mutations are not unique to ameloblastoma and are shared by other odontogenic tumors with ameloblastic morphology. Oral Oncol. 2015;51(10):e77–8.
9 Agaimy A, Skalova A, Franchi A, Alshagroud R, Gill AJ, Stoehr R, Baumhoer D, et al. Ameloblastic fibrosarcoma: clinicopathological and molecular analysis of 7 cases highlighting frequent BRAF and occasional NRAS mutations. Histopathology. 2020;76(6):814–82.
10 Mobark NA, Alharbi M, Alhabeeb L, AlMubarak L, Alaljelaify R, AlSaeed M, et al. Clinical management and genomic profiling of pediatric low-grade gliomas in Saudi Arabia. PLoS One. 2020;15(1):e0228356.
11 Servato JPS, Faria PR, Ribeiro CV, Cardoso SV, Faria PR, Dias FL, et al. Ameloblastic fibrosarcoma: a case report and literature review. Braz Dent J. 2017;28(2):262–72.
12 Maji S, Ghosh I. Ameloblastic fibrosarcoma in pregnancy: an unreported entity. Indian J Surg Oncol. 2019;10(1):180–3.
13 You Z, Xu LL, Li XF, Zhang JY, Du J, Sun LS. [BRAF gene mutations in ameloblastic fibromas]. Beijing Da Xue Xue Bao Yi Xue Ban. 2019;51(1):4–8.
14 Kheder ES, Hong DS. Emerging targeted therapy for tumors with NTRK fusion proteins. Clin Cancer Res. 2018;24(23):5807–14.
15 Zaman A, Wu W, Bivona TG. Targeting oncogenic BRAF: past, present, and future. Cancers. 2019;11(8):1197.
16 Rizzo A, Pantaleo MA, Saponara M, Nannini M. Current status of the adjuvant therapy in uterine sarcoma: a literature review. World J Clin Cases. 2019 Jul 26;7(14):1753–63.
17 Astolfi A, Nannini M, Indio V, Schipani A, Rizzo A, Perrone AM, et al. Genomic database analysis of uterine leiomyosarcoma mutational profile. Cancers. 2020 Aug;12(8):2126.
18 Rizzo A, Nannini M, Astolfi A, Indio V, De Iaco P, Perrone AM, et al. Impact of chemotherapy in the adjuvant setting of early stage uterine leiomyosarcoma: a systematic review and updated meta-analysis. Cancers. 2020 Jul;12(7):1899.